Breast Cancer in Male-to-Female Transgender Patients: A Case for Caution

Maryam Sattari

Clinical Practice Points

- Male-to-female (MTF) transsexual individuals receive hormonal treatment (HT) for acquisition and maintenance of female secondary sex characteristics.
- Rare, but serious, complications associated with long-term HT have been reported.
- Although HT is usually initiated in specialized centers, long-term maintenance is often through more conveniently located primary care providers. Thus, clinicians should be familiar with the potential complications of long-term HT.
- The case of a 60-year-old MTF transgender individual diagnosed with breast cancer after 8 years of HT is presented, with a summary of the related data, discussion of the reported incidence of hormone-sensitive malignancies in MTF transgender patients, and recommendations for monitoring and screening during and after HT.
- This case highlights several issues for MTF transgender patients, and physicians caring for these patients should discuss with them the relevant cancer screening protocols. In addition, the prolactin level should be monitored in subjects taking long-term estrogen.
- An important unanswered question is the age at which cross-sex hormone administration can be responsibly discontinued without inducing an unacceptable risk of osteoporosis and bone fractures.
- Additional reporting of cases such as ours should be encouraged, because true insight can only come from reporting adverse effects in the medical data.

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Introduction

A male-to-female (MTF) transsexual individual has normal male somatic sexual differentiation but is convinced that he is actually a member of the female gender and experiences an irresistible urge to be female hormonally, anatomically, and psychosocially.[1] MTF transsexual individuals might take a variety of nonhormonal and hormonal medications and undergo various cosmetic procedures and gender-reassignment surgery.[1] Hormonal treatment (HT) is initiated for acquisition of female secondary sex characteristics and is continued after gender-reassignment surgery to avoid bone loss and symptoms of sex hormone deficiency.[1,2] Although HT is usually initiated in specialized centers, long-term maintenance is often through more conveniently located primary care providers. Rare, but serious, complications associated with long-term estrogen therapy have been reported.[3] As such, it is important for all primary care providers to be familiar with the potential complications of long-term HT. A case is presented of a MTF transsexual patient, who developed breast cancer after gender-reassignment surgery and while taking estrogen therapy. The goal of the present report is to raise awareness about hormone-sensitive malignancies in MTF transsexual individuals and provide recommendations for long-term treatment and screening after gender-reassignment surgery to avoid unjustified delays in diagnosis and treatment.

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Case Report

A 52-year-old genetically male transsexual patient started HT. One year later (age 53 years), she underwent MTF gender reconstruction surgery, including orchiectomy and construction of a neovagina, and auxiliary cosmetic surgeries and procedures. She continued HT for 7 more years, when screening mammography revealed a right areolar mass. Excisional biopsy confirmed malignancy, and she underwent a modified radical mastectomy with immediate reconstruction for stage 1, T1cN0M0, infiltrating ductal carcinoma breast cancer that was estrogen receptor positive, progesterone receptor positive, and human epidermal growth factor

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receptor 2 negative, grade 2, with lymphovascular invasion. Two sentinel nodes were negative. HT was discontinued, and patient began taking tamoxifen. The 5-year follow-up period was event free.

The test results for BRCA 1 and 2 mutation were negative. The patient did not have a personal history of Klinefelter syndrome or undescended testes. Her family history was negative for breast and ovarian cancer. She denied using tobacco products or illicit drugs but admitted to consuming 2 to 3 glasses of wine daily for $\geq$ 20 years. Because she was genetically male, she had never menstruated nor borne children.

Discussion

Breast cancer is uncommon in males, with an approximate incidence of 1 in 100,000.[4] The peak incidence of male breast cancer occurs at age 68 to 71 years, approximately 5 to 10 years older than in women.[4] Although most men with breast cancer will have no identifiable risk factors, several have been identified, including BRCA gene mutations, family history, androgen deficiency, and estrogen exposure.[4] Whether the present patient's cross-sex HT contributed to the development of breast cancer is unknown. In the absence of a family history of breast cancer, her only other identifiable risk factor was alcohol consumption.

Although it is biologically plausible that continuous estrogen therapy would increase the risk of breast cancer in MTF transgender patients, a search of the published studies from 1966 to 2014 revealed only 7 publications, with, altogether, 10 cases of breast cancer in MTF transsexuals aged 30 to 58 years.[5-11] All the patients had received long-term (5-36 years) HT (Table 1). Of the 7 cases with estrogen receptor status reported, 5 were negative and 2 positive using immunohistochemistry. One case was presumed to be primary breast cancer in a patient with poorly differentiated carcinoma in the lymph nodes 10 years after removal of a benign breast tumor.[11] Three cases, including a secretory carcinoma, malignant fibroepithelial tumor, and triple negative breast carcinoma, might not have been be related to estrogen use.[8,10,11] The other cases occurred at a relatively young age after estrogen exposure.

It seems that breast cancer in MTF transgender patients is either rare or underreported. It is also possible that the duration of exposure to HT might have been too short for the associated breast cancers to manifest themselves, since the first documented HT of transsexuals started only in the 1970s.[1] Routine mammography for MTF individuals has been suggested because of their exposure to long-term, high-dose estrogen.[2] Because aging and estrogen exposure are factors in the development of breast cancer, a pertinent discussion with each MTF transgender individual is the age at which HT should be terminated. It is also important for physicians to recognize the importance of estrogen therapy in bone health, because these patients are often androgen deficient. Strong consideration should be given to measures, such as regular weightbearing exercise and vitamin D and calcium supplementation, to prevent osteoporosis.[2] Experts have also recommended a baseline dual-energy x-ray absorptiometry (DEXA) scan to measure bone mineral density.[2] If estrogen therapy is discontinued, such as was the case for our patient, DEXA should be repeated every 1 or 2 years to assess for osteoporosis.[2]

Table 1 Breast Cancer in Male-to-Female Transsexual Subjects Treated With Androgen Deprivation and Estrogens

Reference	Age (years)	Hormone Use	Breast Tumor Type
Symmers,[5] 1968	30	Oral contraceptives for about 5 years	Adenocarcinoma + metastases; ER status not reported
Symmers,[5] 1968	30	Unknown	Intraductal adenocarcinoma + metastases; ER status not reported
Pritchard et al,[6] 1988	35	Estrogens for 10 years	High-grade ductal carcinoma; ER^-
Ganly and Taylor,[7] 1995	36	14-years Conjugated estrogens 0.625 mg/d	Invasive ductal carcinoma; ER^-
Grabellus et al,[8] 2005	46	Estrogens for about 8 years	Secretory carcinoma ETV6-NTRK3 gene fusion; ER^-
Dhand and Dhaliwal,[9] 2010	58	Estrogens for 11 years	Needle aspiration, ER^+, PR^+, + metastases
Pattison and McLaren,[10] 2013	43	Estrogens for 13 years	Invasive ductal carcinoma + metastases; ER^-, PR^-, $HER2^-$
Gooren et al,[11] 2013	56	Estrogen for about 7 years	Poorly differentiated carcinoma 10 years after removal of a benign breast tumor; ER status not reported
Gooren et al,[11] 2013	57	Estrogen for 36 years	Ductal carcinoma; ER^+, PR^-, $HER2^-$
Gooren et al,[11] 2013	53	Unknown but $\geq$8 years	Phyllodes, ER^-

Abbreviations: ER = estrogen receptor; ETV6 = ETS variant gene 6; HER-2 = human epidermal growth factor receptor 2; NTRK3 = neurotrophic tyrosine kinase receptor, type 3; PR = progesterone receptor.

Another hormone-sensitive malignancy reported in MTF individuals is prostate cancer.[3] The prostate is usually not removed with sex reassignment surgery, because prostatectomy is surgically cumbersome and associated with possible complications.[1] Although androgen deprivation results in prostate volume reduction and estrogen exposure is not thought to induce hyperplasia or (pre)malignancy, benign prostatic hyperplasia, requiring transurethral prostate resection, has been reported in MTF subjects after orchiectomy and HT.[12] The only cases of prostate cancer reported in published studies in MTF individuals have been among subjects who started HT after 50 years of age.[13-15] Consideration should be given to the discussion of the risks and benefits of prostate cancer screening, just as would normally occur with male patients, especially for subjects who started HT later in life and for those with a family history of prostate cancer.[3]

Lactotroph adenoma (prolactinoma) is another rare hormone-sensitive malignancy, with 5 cases reported to date in MTF individuals receiving high-dose estrogen therapy.[3,16-18] A more common complication of continuous estrogen therapy in MTF individuals has been hyperprolactinemia, and consideration should

be given to monitoring the serum prolactin levels in MTF individuals taking long-term HT.[3]

Conclusion

Although current observational studies have suggested that cross-sex hormone administration to MTF transsexuals is acceptably safe in the short term, the safety and potential risks in the longer term are unknown at present. Theoretically, as the transsexual population receiving long-term HT starts to age, a greater incidence of hormone-related complications can be expected in MTF transgender individuals in the future. Additional reporting of cases such as the present case should be encouraged, because true insight can only come from the reporting of adverse effects in medical studies. Another important unanswered question is the age at which cross-sex HT can be responsibly discontinued without inducing an unacceptable risk of osteoporosis and bone fractures.

The present case has highlighted several issues for MTF transgender patients. Physicians caring for these patients should discuss with them the relevant cancer screening protocols, including breast and prostate cancer. In addition, the prolactin level should be monitored in subjects taking long-term estrogen. Just as with other patients, lifestyle modifications, including tobacco cessation, avoidance of excessive alcohol use, regular physical activity, and healthy dietary habits, should be emphasized. If estrogen therapy, pivotal in the maintenance of bone integrity, is discontinued, consideration should be given to the prevention and treatment of osteoporosis and bone fractures.

Disclosure

The author has no financial relationship or potential conflicts of interest to declare.

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